REMARKS

Claims 1, 8, 10-16, 33 and 34 are pending. Claims 1, 8 and 10 have been amended. Claims 3-7, 9, 17-32 and 35-40 have been cancelled. No new matter has been added.

Rejection Under 35 U.S.C. §112, second paragraph

Claims 1, 3-16 and 33-34 are rejected under 35 U.S.C. §112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

In particular, claims 1, 3-16 and 33-34 are rejected "because it is not clear what constitutes a reference standard." In addition, claims 1, 3-16 and 33-34 are rejected "because the meaning of the term 'statistically significant' is a relative term." Claim 1 has been amended to recite "a reference standard that is statistically significant between subjects diagnosed with prostate cancer and having recurrence and subjects diagnosed with prostate cancer that do not have recurrence". The meaning of this phrase in the claims is clear. The reference standard is PSMA expression levels in a primary tumor of a subject diagnosed with prostate cancer that does not have recurrence. As shown in, for example, Perner et al. and Ross et al. (cited in the previous reply), the meaning of statistically significant is clear to one of ordinary skill in the art. Applicants assert that one of skill in the art could, using standard statistics, determine statistically significant differences between expression levels of a given protein between the two patient populations. As demonstrated by the references cited in the previous reply, this is not a relative term. Therefore, Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. §112, first paragraph

Claims 1, 3-16 and 33-34 are rejected under 35 U.S.C. §112, first paragraph "for lack of a clear written description of PSMA." Applicants disagree with this rejection but in the interest of expediting prosecution have amended the claims to recite specific amino acid sequences for human PSMA. The amendment to the claims obviates this rejection.

Claims 1, 3-16 and 33-34 are further rejected under 35 U.S.C. §112, first paragraph, "for lack of enablement."

Specifically, the Office alleges that "Applicant is required to amend the disclosure to include the material incorporated by reference."

Applicants have amended the specification to incorporate the sequences of human PSMA, thereby obviating this rejection.

Claims 1, 3-16 and 33-34 are also rejected "for lack of enablement" for the "determination of risk of prostate cancer recurrence."

Applicants respectfully traverse this rejection. Applicants note that the claims as amended recite that the sample is from a primary tumor of a subject diagnosed with prostate cancer. Applicants have clearly provided sufficient evidence of the correlation between PSMA expression levels in a primary tumor and risk of recurrence in subjects diagnosed with prostate cancer.

Applicants have demonstrated that PSMA expression is an independent predictor of prostate cancer recurrence. The present application describes a multivariate analysis of biopsy samples from one hundred and thirty six patients who underwent a radical prostectomy, determined PSMA expression levels at the time of the prostectomy and tracked those patients to determine which patients had prostate cancer recurrence. From this data, Applicants were able to demonstrate that PSMA expression levels at the time of diagnosis significantly differ between patients that later have recurrence and those who do not.

In the last reply, Applicants submitted additional evidence that corroborated the correlation between PSMA expression levels in the primary tumor of patients having prostate cancer and prostate cancer recurrence. Perner et al. (2007) Human Pathology 38:696-701, submitted previously, performed univariate and multivariate analysis of PSMA expression levels on biopsy samples from patients diagnosed with prostate cancer. This study evaluated biopsy samples from the primary tumor of 450 patients with prostate cancer. Consistent with the data provided in the present application, Perner et al. report that "high PSMA levels were associated

with significant increase in PSA recurrence ... [and] this was independent of clinical parameters." The Office argues with regard to the data provided by Perner et al. that it is unknown "whether such data could be used for predicting recurrence in an unknown population of treated patients, who are in remission." Since the claims require determining PSMA levels in a sample from a **primary tumor** of a **patient having prostate cancer**, the claims do not cover analyzing a subject in remission for PSMA levels.

Applicants also cited a press release in the previous reply where a third party concludes from Applicants' data that "we believe that the publication of clinical data showing overexpression of PSMA in primary cancer ... independently predicts disease recurrence." See the Cytogen Corporation Press Release dated January 5, 2004. The Office alleges that the press release "cannot be evaluated since there is no data accompanying the press release." This is not the case, as stated in the previous reply and reiterated here, the conclusions made in the press release were based upon the data provided in the present application and in the Ross et al. reference from which the present application was derived. Thus, a third party evaluating Applicants' data concluded that overexpression of PSMA in primary cancer independently predicts disease recurrence.

However, the Office continues to maintain that because there is contradictory art concerning whether PSMA levels are predictive of recurrence in prostate cancer, Applicants must provide "**validation** of the data against a prospective patient population." Applicants disagree.

First, Applicants would like to point out that the claims recite that the sample is from the primary tumor of a patient population diagnosed with prostate cancer. This is the exact patient population from which Applicants derived the data that correlated high PSMA expression levels with prostate cancer recurrence. This is also the same patient population that was evaluated by others who have corroborated Applicants' findings.

The Office continues to cite the Tockman et al. and the Vandesompele et al. references to support the assertion that confirmation "of marker predictive value in prospective patient population trials" is necessary. However, both of these references are analyzing proteins as

predictive markers for early detection of primary cancers and not for **recurrence in a patient population diagnosed with a cancer**. For example, Tockman et al. were evaluating a marker in a patient population having breast cancer to assess the value of the marker in a patient population that does not yet have breast cancer. See, e.g., page 2716 of Tockman et al. which discusses diagnosing cancer "well in advance of clinical cancer". Thus, Tockman et al. were deriving their data from a patient population, i.e., patients having breast cancer, different than the patient population in which the marker was going to be used, i.e., patients not yet diagnosed with clinical cancer. As provided above, Applicants' data was derived from the same patient population as that in which the marker will be used, namely patients diagnosed with prostate cancer. Therefore, the need for prospective patient population validation for Tockman et al. and Vandesompele et al., does not translate to a need for such information for the present invention.

The Office cites Bostwick et al., Beckett et al., and Thomas et al. as contradictory to Applicants' data in order to argue that the claimed methods are not enabled. However, the claims require the sample be from the primary tumor whereas both Beckett et al. and Thomas et al. were analyzing serum for circulating PSMA levels. Applicants' data as well as all of the evidence cited by Applicants in the previous reply were derived from analyzing PSMA levels from a primary tumor. Since the data from both Beckett et al. and Thomas et al. were based upon circulating PSMA levels versus PSMA levels from a primary tumor as currently claimed, these references are not relevant to the enablement of the current claims.

The only remaining reference cited by the Office as contradictory is Bostwick et al. published ten years ago. In addition to the two exhibits cited in the previous reply, Applicants attach an additional post filing exhibit (Cytogen Press Release, dated May 22, 2006) that support Applicants' finding that PSMA expression levels in primary tumor samples predict prostate cancer recurrence. In fact, Applicants were unable to find any evidence since Applicants' invention that contradicted Applicants' findings. In view of the overwhelming evidence to support Applicants' finding (in contrast to the one ten year old reference cited by the Office), there is sufficient guidance provided in the present application to enable to claimed invention.

For the reasons provided above, Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. §102(b)

Claims 1-3, 5-6 and 11-16 are rejected under 35 U.S.C. §102(b) as "being anticipated by Murphy et al, 1998 (Urology, 51:89-97)." In the previous reply, Applicants pointed out that Murphy et al. do not teach or suggest that at any particular stage of the disease there can be statistically significant variations between patients to assess the risk of recurrence in a subset of the patients. The Office maintained its rejection asserting that "Murphy et al. teach standard errors for PSMA data in remission patients, which are well into the ranges of 0.02 or 0.03 (table V, on page 94), and thus are clearly statistically significant."

Applicants respectfully traverse this rejection. The claims, as amended, are directed to methods of determining if a subject diagnosed with prostate cancer is at risk for prostate cancer recurrence by determining if PSMA is over expressed in the primary tumor. Applicants were the first to realize that PSMA expression levels in the primary tumor at the time of diagnosis significantly differ between patients having prostate cancer that later have recurrence and patients having prostate cancer which do not.

Murphy et al. disclose analyzing circulating PSMA levels from serum samples. Murphy et al. demonstrate that PSMA levels increased in patients **at the time of recurrence** as compared to patients that did not have recurrence. That is not the same as determining from the primary tumor whether a patient will have recurrence in the future. Nothing from the Murphy et al. reference teaches or suggests that PSMA expression levels in the primary tumor of a subject having prostate cancer can assess the patient's risk for recurrence in the future. Therefore, Applicants respectfully request that this rejection be withdrawn.

An extension fee is being paid concurrently by deposit account authorization. Please charge any deficiency to Deposit Account No. 50/2762, referencing attorney docket number M2051-700410.

Respectfully submitted,

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